

=> d his

(FILE 'HOME' ENTERED AT 09:07:30 ON 01 JUN 2006)

FILE 'CAPLUS, BIOSIS, MEDLINE' ENTERED AT 09:08:07 ON 01 JUN 2006

L1 644567 S INSULIN  
L2 2280313 S DERIVATIVE?  
L3 9988 S L1 (L) L2  
L4 66761 S LIPOPHIL?  
L5 92 S L3 (L) L4  
L6 51 DUP REM L5 (41 DUPLICATES REMOVED)  
L7 39 S L6 AND PY<2002  
L8 145 S L3 AND HEXAMER?  
L9 102 DUP REM L8 (43 DUPLICATES REMOVED)  
L10 71 S L9 AND PY<1998  
L11 59 S L10 AND PY<1996  
L12 0 S L9 AND LIPOPHILIC  
L13 0 S L9 AND LIPOHIL?  
L14 3 S L9 AND LIPO?  
L15 0 S L5 AND HEXAMER?  
L16 19 S L5 AND STAB?  
L17 0 S L16 AND PROLOGN  
L18 0 S L16 AND LIFE  
L19 1 S L16 AND TERMIN?  
E MARKUSSEN JAN /AU  
E HAVELUND SVEND /AU  
L20 88 S E3  
E MARKUSSEN JAN /AU  
L21 116 S E3  
E BRANDT JAKOB /AU  
L22 44 S E3  
E HANSEN PETER /AU  
E KURTZHALS PETER /AU  
L23 44 S E3  
L24 33 S L20 (L) L21  
L25 3 S L22 (L) L23  
L26 3 S L24 AND L22  
L27 15 S L24 AND L23  
L28 10 DUP REM L27 (5 DUPLICATES REMOVED)  
L29 5 S L28 AND INSULIN AND DER?

=

L29 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

TI **Insulin derivatives**

IN **Markussen, Jan; Jonassen, Ib; Havelund, Svend; Brandt, Jakob; Kurtzhals, Peter; Hansen, Per Hertz; Kaarsholm, Niels Christian**

PY 1996  
1996  
1996  
2000  
1998  
1998  
2003  
1999  
1999  
2002  
2002  
2003  
1997  
2001  
2002  
2003  
2004

SO PCT Int. Appl., 58 pp.  
CODEN: PIXXD2

TI **Insulin derivatives**

IN **Markussen, Jan; Jonassen, Ib; Havelund, Svend; Brandt, Jakob; Kurtzhals, Peter; Hansen, Per Hertz; Kaarsholm, Niels Christian**

AB **Insulin derivs. in which a lipophilic group having from 12 to 40 carbon atoms is attached to the  $\alpha$ -amino group of the . . . the carboxy group of the C-terminal amino acid in the B-chain have a protected profile of action. Thus, LysB30(N $\epsilon$ -tetradecanoyl)ThrB29 human insulin was prepared via polymerase chain reaction (PCR) and reaction with tetradecanoic acid N-hydroxysuccinimide ester.**

ST **insulin tetradecanoyl prepn**

IT 11061-68-ODP, Human insulin, derivs. 184181-38-2P  
184181-40-6P 184181-41-7P 184181-43-9P 184181-44-0P 184181-47-3P  
184181-61-1P  
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)  
(preparation of insulin derivs.)

IT 184181-45-1P 184181-49-5P 184181-50-8P 184181-51-9P 184181-52-0P  
184181-54-2P 184181-56-4P 184181-59-7P 184181-62-2P 184181-64-4P  
184246-94-4P  
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of insulin derivs.)

IT 184181-53-1P 184181-55-3P 184181-57-5P 184181-60-0P 184181-63-3P  
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of insulin derivs.)

IT 69888-86-4 120177-51-7 184045-66-7 184045-67-8 184181-58-6  
184493-04-7 184493-05-8 184493-06-9 184493-07-0 184493-08-1  
184493-09-2 184493-10-5 184493-11-6 184493-12-7 184493-13-8  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of insulin derivs.)

IT 184181-46-2P 184181-48-4P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of insulin derivs.)

L29 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

TI **Albumin Binding and Time Action of Acylated Insulins in Various Species**

AU **Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib; Kiehr, Benedicte; Ribel, Ulla; Markussen, Jan**

PY 1996

SO **Journal of Pharmaceutical Sciences (1996), 85(3), 304-8**

- TI Albumin Binding and Time Action of Acylated Insulins in Various Species
- AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib; Kiehr, Benedicte; Ribel, Ulla; Markussen, Jan
- AB Insulins acylated with fatty acids at the  $\epsilon$ -amino group of N $\epsilon$ B29 constitute a new class of insulin analogs, which are prolonged-acting due to albumin binding. In the present study it is shown that the affinity of fatty acid acylated insulins for albumin varies considerably ( $>50$ -fold) among species. The relative affinities of acylated insulin for albumin in human, pig, and rabbit serum are about 1:1.5:35. The severalfold higher binding affinity in rabbit serum than . . . pig serum and human serum, the pig model should provide a useful estimate of the degree of protraction of acylated insulin in humans. The results emphasize that species differences in ligand binding can be of major importance in the preclin. evaluation.
- ST acylated insulin albumin binding
- IT Rabbit  
Swine  
(albumin binding and time action of acylated insulins in various species)
- IT Albumins, biological studies  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(albumin binding and time action of acylated insulins in various species)
- IT 11061-68-0D, Human insulin, N $\epsilon$ B29-fatty acylated derivs. 169148-58-7 169148-62-3 169148-63-4  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(albumin binding and time action of acylated insulins in various species)
- L29 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
- TI Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo
- AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib; Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; Markussen, Jan
- PY 1995
- SO Biochemical Journal (1995), 312(3), 725-31  
CODEN: BIJOAK; ISSN: 0264-6021
- TI Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo
- AU Kurtzhals, Peter; Havelund, Svend; Jonassen, Ib; Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; Markussen, Jan
- AB Albumin is a multifunctional transport protein that binds a wide variety of endogenous substances and drugs. Insulins with affinity for albumin were engineered by acylation of the  $\epsilon$ -amino group of LysB29 with saturated fatty acids containing 10-16 carbon atoms. The association consts. for binding of the fatty acid acylated insulins to human albumin are in the order of  $10^4$ - $10^5$  M $^{-1}$ . The binding apparently involves both non-polar and ionic interactions with the protein. The acylated insulins bind at the long-chain fatty acid binding sites, but the binding affinity is lower than that of the free fatty. . . relatively small degree on the number of carbon atoms in the fatty acid chain. Differences in affinity of the acylated insulins for albumin are reflected in the relative timing of the blood-glucose-lowering effect after s.c. injection into rabbits. The acylated insulins provide a breakthrough in the search for soluble, prolonged-action insulin preps. for basal delivery of the hormone to the diabetic patient. We conclude that the biochem. concept of albumin binding can be applied to protract the effect of insulin, and suggest that derivatization with albumin-binding ligands could be generally applicable to prolong the action profile of peptide drugs.
- ST albumin binding acylated insulin prolonged action

IT Blood sugar  
(albumin binding of **insulins** acylated with fatty acids  
prolong blood sugar-lowering action)  
IT Fatty acids, biological studies  
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES  
(Uses)  
(albumin binding of **insulins** acylated with fatty acids  
prolong blood sugar-lowering action)  
IT Albumins, biological studies  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(albumin binding of **insulins** acylated with fatty acids  
prolong blood sugar-lowering action)  
IT 9004-10-8D, **Insulin**, acylated with fatty acids  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)  
(albumin binding of **insulins** acylated with fatty acids  
prolong blood sugar-lowering action)

L29 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
TI **Insulin derivatives.**  
AU **Markussen, Jan** [Inventor, Reprint Author]; **Jonassen, Ib**  
[Inventor]; **Havelund, Svend** [Inventor]; **Brandt, Jakob**  
[Inventor]; **Kurtzhals, Peter** [Inventor]; **Hansen, Per Hertz**  
[Inventor]; **Kaarsholm, Niels Christian** [Inventor]  
PY 2003  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
(Sep 16 2003) Vol. 1274, No. 3. <http://www.uspto.gov/web/menu/patdata.html>  
. e-file.  
ISSN: 0098-1133 (ISSN print).  
TI **Insulin derivatives.**  
AU **Markussen, Jan** [Inventor, Reprint Author]; **Jonassen, Ib**  
[Inventor]; **Havelund, Svend** [Inventor]; **Brandt, Jakob**  
[Inventor]; **Kurtzhals, Peter** [Inventor]; **Hansen, Per Hertz**  
[Inventor]; **Kaarsholm, Niels Christian** [Inventor]  
AB The present invention relates to **insulin derivatives**  
in which a lipophilic group having from 12 to 40 carbon atoms is attached  
to the alpha-amino group of the. . .  
IT Major Concepts  
Pharmacology  
IT Chemicals & Biochemicals  
**insulin derivatives**: antidiabetic-drug,  
hormone-drug, metabolic-drug  
RN 9004-10-8D (**insulin derivatives**)

L29 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
TI **Insulin derivatives.**  
AU **Markussen, Jan** [Inventor, Reprint author]; **Jonassen, Ib**  
[Inventor]; **Havelund, Svend** [Inventor]; **Brandt, Jakob**  
[Inventor]; **Kurtzhals, Peter** [Inventor]; **Hansen, Per Hertz**  
[Inventor]; **Kaarsholm, Niels Christian** [Inventor]  
PY 2001  
SO Official Gazette of the United States Patent and Trademark Office Patents,  
(June 26, 2001) Vol. 1247, No. 4. e-file.  
CODEN: OGUPE7. ISSN: 0098-1133.  
TI **Insulin derivatives.**  
AU **Markussen, Jan** [Inventor, Reprint author]; **Jonassen, Ib**  
[Inventor]; **Havelund, Svend** [Inventor]; **Brandt, Jakob**  
[Inventor]; **Kurtzhals, Peter** [Inventor]; **Hansen, Per Hertz**  
[Inventor]; **Kaarsholm, Niels Christian** [Inventor]  
AB The present invention relates to **insulin derivatives**  
in which a lipophilic group having from 12 to 40 carbon atoms is attached  
to the alpha-amino group of the. . .  
IT Major Concepts  
Pharmacology  
IT Chemicals & Biochemicals  
**insulin derivatives**: hormone-drug

L19 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Trials of lipid modification of peptide hormones for intestinal delivery  
AU Muranishi, Shozo; Murakami, Masahiro; Hashidzume, Minoru; Yamada, Keigo;  
Tajima, Shigeru; Kiso, Yoshiaki  
PY 1992  
SO Journal of Controlled Release (1992), 19(1-3), 179-88  
CODEN: JCREEC; ISSN: 0168-3659  
AB . . . study the intestinal delivery of peptide, three typical peptide hormones with different mol. wts., TSH-releasing hormone (TRH), tetragastrin (TG) and **insulin**, were used. With the aim of increasing peptide **lipophilicity**, these peptides were chemical modified by attaching fatty acid moieties (acyl chains) to their amino **termini**; this was achieved without marked loss of pharmacol. activities. By reverse-phase HPLC, the synthesized peptide analogs, lauroyl-TRH, caproyl- and lauroyl-TG, and B1-monopalmitoyl- and B1, B29-dipalmitoyl-**insulin**, were confirmed to be more **lipophilic** than their parent peptides. These analogs retained more than 64% of the pharmacol. activities of the parent peptides, as assessed following i.v. injection in rats. The results obtained showed that the **lipophilic derivs.** were more suitable for intestinal absorption than the parent peptides and that the **stabilities** of some **derivs.** against intestinal enzymic degradation were improved. These findings suggest that, by appropriate lipid modification of the amino-**terminus** of peptides, it may be feasible to improve their intestinal delivery characteristics and their protective capabilities against enzymic degradation

L14 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN  
 TI Soluble, prolonged-acting **insulin derivatives**. II.  
 Degree of protraction and crystallizability of **insulins**  
 substituted in positions A17, B8, B13, B27 and B30  
 AU Markussen, J.; Diers, I.; Engesgaard, A.; Hansen, M. T.; Hougaard, P.;  
 Langkjaer, L.; Norris, K.; Ribel, U.; Soerensen, A. R.; et al.  
 PY 1987  
 SO Protein Engineering (1987), 1(3), 215-23  
 CODEN: PRENE9; ISSN: 0269-2139  
 TI Soluble, prolonged-acting **insulin derivatives**. II.  
 Degree of protraction and crystallizability of **insulins**  
 substituted in positions A17, B8, B13, B27 and B30  
 AB . . . . by B27 lysine or arginine substitutions and by B13 glutamine.  
 The B27 residue is located on the surface of the **hexamer**, so a  
 basic residue in this position presumably promotes the packing of  
**hexamers** at neutral pH. The B13 residues cluster in the center of  
 the **hexamer**. When the electrostatic repulsive forces from 6  
 glutamic acid residues are abolished by substitution with glutamine, a  
 stabilization of the **hexamer** can be envisaged. The biol.  
 potency of insulins was measured in the free fat cell assay and in the  
 mouse. . . .  
 ST mutagenesis gene **insulin deriv** prepn; **insulin**  
**deriv** structure activity; crystal structure **insulin**  
**deriv**  
 IT Chains, chemical  
 (helical conformation of, of **insulin derivs.**)  
 IT Blood sugar  
 (**insulin derivs.** effect on, mol. structure in  
 relation to)  
 IT Lipids, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (metabolism of, by adipocyte, **insulin derivs.** effect  
 on, mol. structure in relation to)  
 IT Bond angle  
 Conformation and Conformers  
 Crystal structure  
 (of **insulin derivs.**)  
 IT Adipose tissue, metabolism  
 (adipocyte, lipid metabolism by, **insulin derivs.** effect  
 on, mol. structure in relation to)  
 IT Molecular structure-property relationship  
 (crystallization, of **insulin derivs.**)  
 IT Molecular structure-property relationship  
 (hydrophobicity, of **insulin derivs.**)  
 IT Molecular structure-biological activity relationship  
 (hypoglycemic, of **insulin derivs.**)  
 IT Molecular structure-biological activity relationship  
 (lipogenic, of **insulin derivs.**)  
 IT 9004-10-8DP, **Insulin, derivs.** 110068-59-2P  
 110068-60-5P 110068-61-6P 110068-62-7P 110068-64-9P 110068-67-2P  
 110068-70-7P 110068-71-8P 110068-72-9P 110068-73-0P 111775-84-9P  
 111775-85-0P 111775-86-1P 111775-87-2P 111775-88-3P 111775-89-4P  
 111775-90-7P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); BIOL (Biological  
 study); PREP (Preparation)  
 (preparation and biol. activity of, mol. structure in relation to)

L14 ANSWER 2 OF 3 MEDLINE on STN  
 TI Long-term comparison of human insulin analogue B10Asp and soluble human  
 insulin in IDDM patients on a basal/bolus insulin regimen.  
 AU Nielsen F S; Jorgensen L N; Ipsen M; Voldsgaard A I; Parving H H  
 PY 1995  
 SO Diabetologia, (1995 May) Vol. 38, No. 5, pp. 592-8.  
 Journal code: 0006777. ISSN: 0012-186X.  
 AB . . . . compared to soluble human insulin. The human insulin analogue  
 B10Asp (mono/dimeric) is absorbed twice as fast as soluble human insulin (

hexameric). A double blind, randomised crossover study with a 1-month run-in period and two 2-month treatment periods was performed in 21. . .

CT  
drug therapy

Double-Blind Method  
Drug Administration Schedule  
Hemoglobin A, Glycosylated: AN, analysis  
Humans  
Injections, Intravenous  
Insulin: AD, administration & dosage  
\*Insulin: AA, analogs & derivatives  
\*Insulin: TU, therapeutic use  
Lipoproteins, HDL Cholesterol: BL, blood  
Lipoproteins, LDL Cholesterol: BL, blood  
Recombinant Proteins: AD, administration & dosage  
Recombinant Proteins: TU, therapeutic use  
Time Factors  
Triglycerides: BL, . . .

CN 0 (Blood Glucose); 0 (Hemoglobin A, Glycosylated); 0 (Lipoproteins, HDL Cholesterol); 0 (Lipoproteins, LDL Cholesterol); 0 (Recombinant Proteins); 0 (Triglycerides); 0 (insulin, Asp(B10)-)

L14 ANSWER 3 OF 3 MEDLINE on STN

TI Semisynthetic des-(B27-B30)-insulins with modified B26-tyrosine.

AU Lenz V; Gattner H G; Sievert D; Wollmer A; Engels M; Hocker H

PY 1991

SO Biological chemistry Hoppe-Seyler, (1991 Jul) Vol. 372, No. 7, pp. 495-504.

Journal code: 8503054. ISSN: 0177-3593.

AB . . . formal transpeptidation product at ArgB22--was formed in one step. Biological in vitro properties (binding to cultured human IM-9 lymphocytes, relative lipogenic potency in isolated rat adipocytes) of all semisynthetic analogues are reported, ranging from slightly decreased to two-fold receptor affinity and. . . typical of native insulin can be observed, and the CD-spectral effects in the near UV spectrum related to association and hexamerization of the native hormone are qualitatively reestablished. The results of this investigation underline the importance of position B26 to the. . .

CT Amino Acid Sequence

Circular Dichroism

Humans

\*Insulin: AA, analogs & derivatives

Insulin: BI, biosynthesis

Molecular Sequence Data

Peptide Biosynthesis

\*Peptide Fragments: BI, biosynthesis

Research Support, Non-U.S. Gov't

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	30801	insulin and derivativ?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L2	3754	hexamer?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L3	0	hexamer*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L4	29	hexamer???	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L5	968	hexamer??	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L6	840	I1 and I2	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L7	108	I6 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L8	49	I6 and @py<"1998"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L9	0	I8 and stab?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L10	19	I8 and life	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L11	43	I8 and composition	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L12	29	I11 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L13	0	I7 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L14	19	I7 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L15	19	I14 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:40



## EAST Search History

L16	17	l15 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L17	25	markussen adj jan	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L18	32	havelund near svend	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L19	8	brandt near jakob	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L20	7	kurtzhals near peter	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L21	50	l17 or l18 or l19 or l20	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L22	50	l21 and insulin	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L23	36	l22 and derivative?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L24	13	l23 and hexameric	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L25	0	l24 and lipo	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L26	0	l24 and lipo*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L27	0	l24 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L28	13	l24 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:47